Minocycline Extended-Release Comparison with Doxycycline for the Treatment of Rosacea: A Randomized, Head-to-Head, Clinical Trial

by ATHANASIOS TSIANAKAS, MD; THOMAS PIEBER, MD; HILARY BALDWIN, MD; FRANZ FEICHTNER, PhD; SHANAVAS ALIKUNJU, PhD; ANIRUDH GAUTAM, MPharm; SRINIVAS SHENOY, MD; PREETI SINGH, MD; and SRINIVAS SIDGIDDI, MD

Dr. Tsianakas is with the Department of Dermatology at Fachklinik Bad Bentheim in Bad Bentheim, Germany. Dr. Pieber is with the Medical University of Graz in Graz, Austria. Dr. Baldwin is with The Acne Treatment and Research Center in Brooklyn, New York. Dr. Feichtner is with the HEALTH Institute of Biomedicine and Health Sciences at Joanneum Research Forschungsgesellschaft mbH in Graz, Austria. Dr. Alikunju is with Dr. Reddy's Laboratories in Hyderabad, India. Mr. Gautam is with Dr. Reddy's Laboratories SA in Basel, Switzerland. Drs. Shenoy, Singh, and Sidgiddi are with Dr. Reddy's Laboratories in Princeton, New Jersey.

J Clin Aesthet Dermatol. 2021;14(12):16–23.

ABSTRACT

OBJECTIVE: Minocycline efficacy for the treatment of papulopustular rosacea (PPR) has not been evaluated in clinical trials at levels demonstrated to stay below the antimicrobial threshold. We assessed the efficacy, safety, and dose response of DFD-29, a minocycline extended-release oral capsule. Two studies are reported (NCT03340961). **METHODS:** A single-center open-label, three-arm, Phase I pharmacokinetic study randomized 24 healthy subjects aged 18 to 45 years to receive 21 days of once-daily dosing with DFD-29 40 or 20mg, or doxycycline 40mg. Blood samples were collected over 24 hours on Days 1 and 21 to plot mean plasma concentration levels. A multicenter Phase II clinical trial randomized 205 subjects with mild-to-severe PPR 1:1:1:1 to receive once-daily DFD-29 40 or 20mg, doxycycline 40mg, or placebo for 16 weeks. Co-primary endpoints were the proportion of subjects achieving treatment success (IGA grade 0 or 1 and ≥2-grade improvement) at Week 16, and a reduction in total inflammatory lesion count at Week 16. **RESULTS:** Pharmacokinetic analysis demonstrated that minocycline plasma levels of DFD-29 40mg were approximately half those of doxycycline 40mg after 21 days, with DFD-29 20mg even lower, demonstrating a dose response. In the Phase II trial, DFD-29 40mg met both co-primary endpoints, achieving IGA treatment success in 66.0 percent subjects versus 11.5 percent placebo ($p<0.0001$), 31.9 percent DFD-29 20mg ($p=0.007$), and 33.3 percent doxycycline 40mg ($p<0.0010$), and a mean reduction in lesion counts of −19.2 versus −7.3 placebo ($p<0.0001$), −12.6 DFD-29 20mg ($p=0.0070$), and −10.5 doxycycline 40mg ($p=0.0004$). **LIMITATIONS:** MIC values and plasma concentrations shown for antibacterial threshold data are mean values; fast absorbers/slow metabolizers could exceed the threshold, causing resistance selection pressure. **CONCLUSION:** DFD-29 40mg demonstrated significantly greater efficacy than placebo, DFD-29 20mg, and doxycycline 40mg at plasma concentrations predicted to be below the antimicrobial threshold for the treatment of PPR.

KEYWORDS: Rosacea, papulopustular rosacea, doxycycline, minocycline

Rosacea is a chronic, relapsing inflammatory condition affecting the central face. This common dermatologic condition has an estimated worldwide prevalence of approximately 5 percent, affecting 16 million people in the United States. [1,2]

Papulopustular rosacea (PPR) is one of four main subtypes of rosacea that have been traditionally used to classify patients for both clinical trials and treatment. The prevalence of PPR has been estimated to be 1 to 3 percent in the general population and 20 to 48 percent in people with rosacea.[3-7]

The traditional diagnostic criteria for PPR was transient papules and/or pustules clustered in the centrofacial region with or without persistent erythema.[8,9] Recently, in recognition that many patients experience signs and symptoms from more than one of the traditional four rosacea subtypes (e.g., erythema and PPR commonly overlap), focus has shifted to a phenotypic description.[10]

Rosacea pathophysiology has not been fully elucidated, but appears to result partly from dysregulation of the innate and adaptive immune systems in response to both genetics and exposure to triggers. Increased levels of leukocytes, macrophages, mast cells, and neutrophils are found in papules and pustules, with concomitant increases in cytokine levels.[11,12]

Recommended treatment for PPR include topical azelaic acid, ivermectin, and/or metronidazole, and the tetracycline class of antibiotics as monotherapy or in combination with topical treatments.[13,14] Tetracyclines, including doxycycline and minocycline, have multiple anti-inflammatory mechanisms of action, including inhibiting the secretion of proinflammatory cytokines, decreasing neutrophil chemotaxis, reducing the production of nitric oxide and reactive oxygen species, reducing phospholipase A2 activity, reducing production of tissue-damaging matrix metalloproteinases, and suppression of the arachidonic acid pathway.[15–22] These actions help to combat the multiple inflammatory processes seen in the pathophysiology of PPR.

While tetracyclines are well known as antibiotics, these anti-inflammatory activities occur at sub-antimicrobial doses. As rosacea is a chronic condition requiring long-term treatment, it is crucial that oral tetracyclines be administered below the antimicrobial

FUNDING: This study was funded by Dr. Reddy's Laboratories.
DISCLOSURES: Dr. Tsianakas has received honoraria as a consultant and speaker from Novartis, Sanofi-Aventis, UCB, Pfizer, Kyowa Kirin, Beiersdorf, Janssen-Cilag, Almirall, Celgene, and LEO Pharma. Dr. Baldwin has received honoraria from Galderma, Mayne, Ortho-Dermatologics, Almirall, EPI Health, and Sun. Dr. Pieber has nothing to disclose. Dr. Feichtner has nothing to disclose. The remaining authors are all employees of Dr Reddy's Laboratories.
CORRESPONDENCE: Srinivas Sidgiddi, MD; Email: srinivassidgiddi@drreddys.com

threshold to prevent selection pressure for bacterial resistance. Currently, the only tetracycline approved for the treatment of PPR is doxycycline 40mg modified-release capsules (Galderma, Fort Worth, Texas).[23] These contain a combination of immediate-release (30mg) and delayed-release (10mg) beads. This formulation has been shown to maintain doxycycline levels below the minimum inhibitory concentration (MIC) of doxycycline-susceptible bacteria.[12] Phase III studies have shown significant improvements in lesion count and Investigator's Global Assessment (IGA) with doxycycline modified-release 40mg, with 15 to 31 percent of subjects achieving an IGA of "clear" or "almost clear" after 16 weeks of daily treatment.[23]

Minocycline has been used for years off-label to treat PPR, but limited evidence-based data support its use. A 16-week comparison of doxycycline modified-release 40mg versus minocycline 100mg in patients diagnosed with PPR concluded that minocycline was noninferior to doxycycline with similar reductions in lesion count.[24] Minocycline extended-release formulation has been approved for the treatment of acne, with recommended dosing at 1mg/kg/day, resulting in lower plasma levels than the nonmodified release formulations of minocycline.[25] The extended-release minocycline 45mg dose was shown to significantly reduce lesion counts in PPR after 12 weeks of daily treatment.[26] However, the dose-related efficacy of subantimicrobial doses of minocycline has not been assessed in rosacea, using the standard co-primary endpoints of IGA treatment success and absolute total inflammatory lesion count reductions.

DFD-29 is a low-dose minocycline extended-release formulation produced at doses well below the approved antimicrobial dose. Two doses of DFD-29 (20- and 40mg) were compared to doxycycline 40mg. It was hypothesized that minocycline would have higher tissue penetration and exposure in the skin than doxycycline modified-release 40mg due to the higher lipophilicity and lower protein binding of minocycline. This study was designed to test the safety and efficacy of DFD-29 for the treatment of PPR compared to both placebo and doxycycline 40mg modified-release.

METHODS

Ethics. Both studies reported here were conducted under the ICH Harmonized Guidelines for Good Clinical Practice, the Declaration of Helsinki, and local regulatory guidelines. Written informed consent was obtained from all study participants.

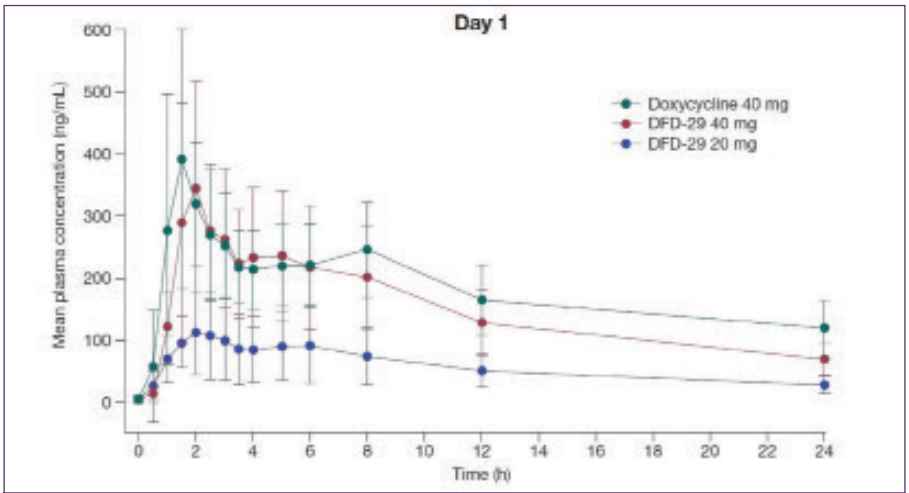

FIGURE 1A. Mean (±SD) plasma profiles of DFD-29 (minocycline) and doxycycline on Day 1

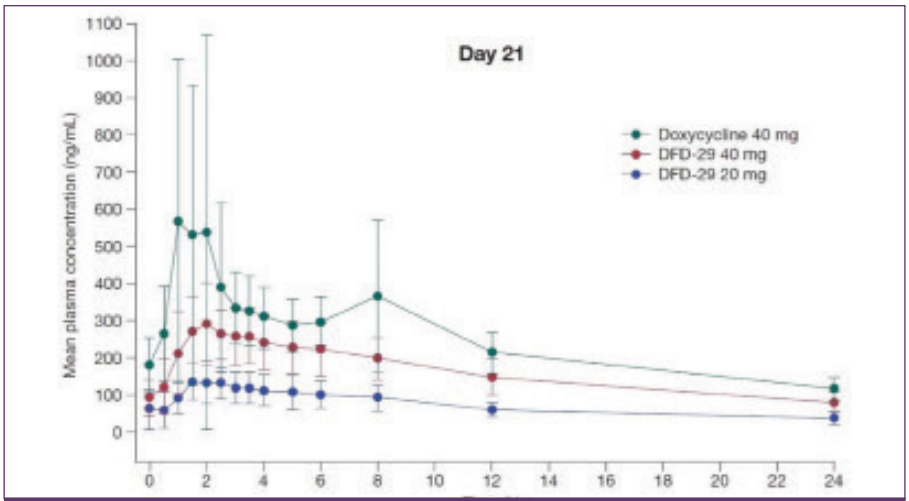

FIGURE 1B. Mean (±SD) plasma profiles of DFD-29 (minocycline) and doxycycline on Day 21

DFD-29 pharmacokinetic study. A single-center, open-label study assessed the systemic pharmacokinetics (PK) of oral DFD-29 (minocycline hydrochloride) extended-release 20mg and 40mg capsules (Dr. Reddy's Laboratories Ltd., India) versus doxycycline 40mg modified-release capsules (Oracea; Galderma International). Male and female subjects aged 18 to 45 years were randomized to receive DFD-29 40mg, DFD-29 20mg, or doxycycline modified-release 40mg once daily for 21 days under fasting conditions (≥8-hour fast before, and 1 hour after, dosing). Plasma samples were taken over 24 hours on Days 1 and 21 for PK analysis.

Phase II study (NCT03340961).

Subjects. Male and female subjects ≥18 years with Fitzpatrick skin types I–III and a diagnosis of PPR were screened. Inclusion criteria included an IGA grade 2–4 (mild–severe), 10 to 40 facial inflammatory lesions (papules and pustules; ≤2 nodules), and a Clinician's Erythema Assessment score of 5 to 20 corresponding to moderate-to-severe erythema. Subjects were excluded if they had used any rosacea treatment, systemic steroids, nephrotoxic drugs, or immunosuppressive medication in the prior 30 days, used systemic retinoids in the prior six months, or had a known tetracycline hypersensitivity. Subjects were assessed as free of any dermatologic or systemic condition that would confound the evaluation of rosacea.

Study design. This was a 16-week, multicenter, randomized, double-blind, Phase II

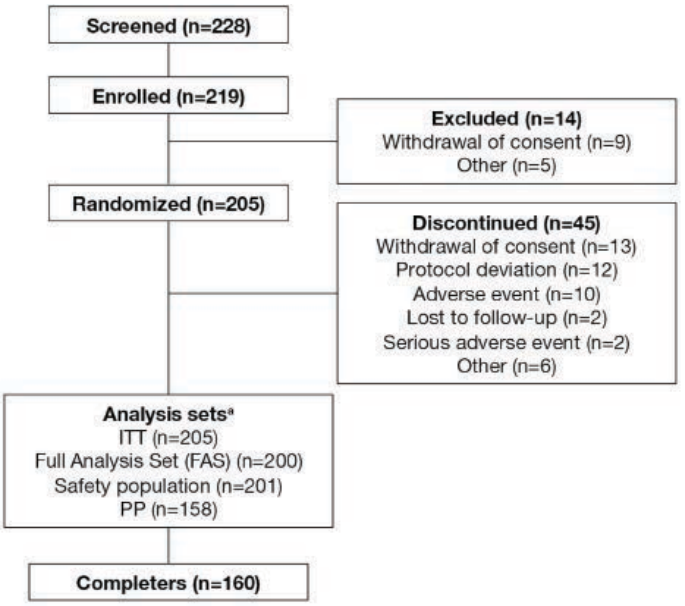

FIGURE 2. Phase II study subject disposition and analysis sets.
[a]ITT population included all randomized subjects dispensed the study drug; FAS included all randomized subjects with at least one post-baseline efficacy assessment; Safety population included all randomized subjects with at least one post-baseline safety assessment; PP population included all subjects who completed the study without protocol deviations

study. This four-arm study randomized subjects 1:1:1:1 to receive DFD-29 40mg, DFD-29 20mg, doxycycline 40mg (Oracea; Galderma, Fort Worth, Texas), or placebo once daily for 16 weeks. Double blinding was ensured by over-encapsulation of all treatments.

Assessments. IGA and inflammatory lesion count were performed on Day 1 (baseline) and at Weeks 4, 8, 12, and 16. The IGA was a modified 0-to-4 scale without erythema:

- 0=clear
- 1=near clear (1–2 papules)
- 2=mild (some papules)
- 3=moderate (moderate number of papules)
- 4=severe (numerous papules).

Weeks 4 through 16 assessments were compared with baseline. The impact of treatment on subjects' quality of life (QoL) was assessed using the rosacea-specific tool RosaQoL at baseline and at Weeks 4, 8, 12, and 16.

Treatment-emergent adverse events (TEAEs), including those leading to discontinuation, as well as serious adverse events (SAEs) were collected through spontaneous reporting, subject questioning, and direct observation. Clinical laboratory tests were conducted at screening, Week 4, and Week 16; vital signs were assessed at each visit. Clinically significant abnormalities of laboratory assessments after screening were recorded as an AE or SAE, as appropriate.

Endpoints. Co-primary endpoints were the proportion of subjects achieving treatment success (IGA grade 0/1 and a ≥2-grade improvement) at Week 16, and the reduction in total inflammatory lesion count (sum of papules, pustules, and nodules) from baseline to Week 16, in the DFD-29 40mg group compared with placebo. Overall treatment success required both co-primary endpoints to be met.

Secondary endpoints included the proportion of subjects achieving a ≥2-grade reduction in IGA at Week 16 versus baseline and median change in RosaQoL score at Week 16.

Statistics. Sample size was determined to demonstrate superiority of DFD-29 over placebo, assuming the treatment effect with DFD-29 to be similar or better than doxycycline 40mg, and utilizing the treatment effects from the doxycycline 40mg Phase III studies. An enrollment of 200 (50/arm) was calculated to adequately power comparison between treatment arms.

For all endpoints, the primary comparison was between DFD-29 40mg and PBO. All other comparisons between DFD-29 groups and doxycycline or placebo were secondary. Primary analyses were carried out on the full analysis set (FAS; randomized subjects who had at least one efficacy evaluation post dose). Intent-to-treat (ITT) and per-protocol (PP) populations were analyzed as secondary evaluations.

Changes in IGA were assessed using χ^2 analyses. Changes in lesion count were assessed using MIXED model, with the investigator as a random factor. Multiple imputation (MI) and last observation carried forward (LOCF) methods were used for handling of missing data for the primary endpoint comparison. The median change in RosaQoL was assessed using the Kruskal–Wallis test. Safety assessments were recorded using descriptive statistics and frequency tables.

RESULTS

PK study. Twenty-four subjects were randomized to receive once daily DFD-29 40 mg, DFD-29 20 mg, or doxycycline 40 mg for 21 days. Mean plasma levels on Day 1 showed similar plasma levels between DFD-29 (minocycline) 40 mg and doxycycline 40 mg, with DFD-29 20 mg levels approximately half of DFD-29 40 mg (Figure 1A). By Day 21, plasma doxycycline exposure (AUC_{0-24}) had increased by approximately one-third from 4377.5 ng.h/mL (SD 1232.31) to 6074.8 ng.h/mL (SD 1979.9). In contrast, DFD-29 maintained relatively stable minocycline levels after three weeks of daily dosing: DFD-29 40mg, Day 1 AUC_{0-24} 3549.6 ng.h/mL (SD 1438.6), Day 21 AUC_{0-24} 3957.6 ng.h/mL (SD 1099.0); DFD-29 20 mg Day 1 AUC_{0-24} 1412.3 ng.h/mL (SD 757.1), Day 21 AUC_{0-24} 1953.9 ng.h/mL (SD 645.8) (Figure 1B).

Phase II study. Altogether, 205 subjects were randomized to receive DFD-29 40mg, DFD-29 20mg, doxycycline 40mg, or placebo, and were included in the ITT population. Of those, 160 completed the study, with 158 included in the PP population. Reasons for discontinuation included withdrawal of informed consent, AEs, and use of prohibited medication (Figure 2). The primary analysis was conducted using the FAS, which included 200 subjects who had at least one post-dose efficacy evaluation.

Demographic and baseline characteristics showed no statistically significant differences between groups (Table 1). All subjects had a baseline IGA of 2–4, with 10 to 40 inflammatory

TABLE 1. Description of facial areas and associated risk levels

CHARACTERISTIC	PLACEBO N=53	DFD-29 40 MG N=53	DFD-29 20 MG N=50	DOX 40 MG N=49	OVERALL N=205
Age, years—median (min, max)	53 (29,59)	46 (22,77)	53 (24,73)	52 (26, 85)	51 (22, 85)
Female, %	50.9%	64.2%	68.0%	59.2%	60.5%
White race, %	100%	100%	100%	100%	100%
IGA score—median (min, max)	3 (2,4)	3 (2,4)	3 (2,4)	3 (2,4)	3 (2,4)
Total inflammatory lesion count—median (min, max)	23 (11,39)	23 (12,39)	23 (11,52)	24 (10,40)	23 (10,52)
RosaQoL score—median (min, max)	73.0 (36,96)	73.0 (39,96)	72.5 (42,92)	66.0 (30,83)	70.0 (30,96)

* DOX, doxycycline; IGA, Investigator's Global Assessment

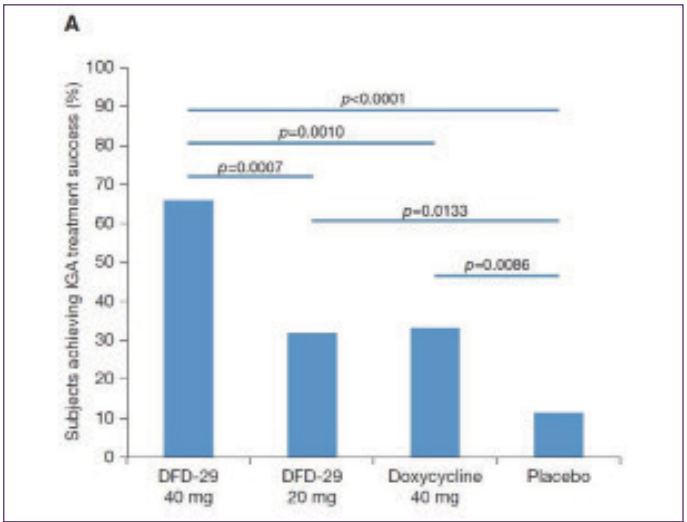

FIGURE 3A. Proportion of subjects achieving treatment success for IGA (defined as a ≥2-grade reduction from baseline with grade 0 or 1 at end of study) at Week 16. FAS shown. χ2 test using MI for missing data.

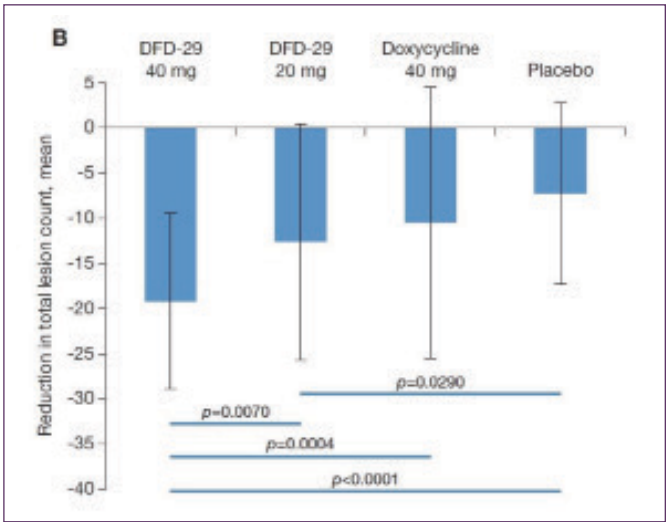

FIGURE 3B. Mean reduction in total of papules, pustules, and nodules from baseline to Week 16. FAS shown with SD. Mixed model using MI for missing data.

lesions and ≤2 nodules on the face.

Primary efficacy endpoints. DFD-29 40mg met both co-primary endpoints of achieving significant IGA treatment success and a reduction in lesion counts compared to placebo at Week 16. A significantly higher proportion of subjects achieved IGA treatment success at 16 weeks with DFD-29 40mg versus placebo (66.04% vs. 11.54%; $p<0.0001$) (Figure 3A). DFD-29 40mg also achieved significantly greater IGA treatment success than both doxycycline 40mg (66.04% vs. 33.33%; $p=0.0010$) and DFD-29 20mg (66.04% vs. 31.91%; $p=0.007$). Statistically significant differences were also found for DFD-29 20mg ($p=0.0133$) and doxycycline 40mg ($p=0.0086$) versus placebo.

The DFD-29 40mg group achieved a significant mean reduction in inflammatory lesions compared to placebo (−19.2 vs. −7.3; $p<0.0001$) (Figure 3B). DFD-29 40mg was also significantly more effective at reducing lesion counts than DFD-29 20mg (−19.2 vs. −12.6; $p=0.0070$) and doxycycline 40mg (−19.2 vs. −10.5; $p=0.0004$). DFD-29 20mg significantly reduced lesion counts compared to placebo (−12.6 vs. −7.3; $p=0.0290$). The reduction in total lesions with doxycycline 40mg was not statistically significant versus placebo ($p=0.1187$).

DFD-29 20mg also achieved a significant treatment effect for both primary endpoints ($p\leq0.0290$). Furthermore, DFD-29 40mg resulted in statistically greater treatment success than the active comparator, doxycycline 40mg, at 16 weeks ($p\leq0.0010$). Results and significant differences for both co-primary endpoints were similar using the MI and LOCF methods handling missing data, and for the ITT and PP population (data not shown), indicating robust support of the data.

Secondary efficacy endpoints. The proportion of subjects achieving a ≥2-grade reduction in IGA at 16 weeks versus baseline was similar to those seen for the co-primary IGA success.

A significantly higher proportion of subjects achieved a ≥2-grade reduction in IGA with DFD-29 40mg versus placebo (69.8% vs. 17.3%; $p<0.0001$), versus DFD-29 20mg (69.8% vs. 36.2%; $p=0.0008$), and versus doxycycline 40mg (69.8% vs. 37.5%; $p=0.0011$). DFD-29 20mg reductions in IGA were also significantly greater than placebo ($p=0.0332$).

Median RosaQoL scores at baseline ranged from 66.0 to 73.0 between groups (self-reported rosacea severity of poor/fair).[27] At 16 weeks, the highest treatment effect was seen with DFD-29 40mg, with a median reduction of 11 points (−11 [min, max: −53, 11]), followed by DFD-29 20mg (−8.0 [−34, 8]), doxycycline 40mg (−3.0 [−30, 25]), and placebo (−1.0 [−37, 19]) (Figure 4). The treatment difference for DFD-29 40mg was statistically significant versus placebo, DFD-29 20mg, and doxycycline 40mg ($p<0.0001$ for all comparisons). DFD-29 20mg and doxycycline 40mg showed a significant reduction in RosaQoL scores versus placebo

TABLE 2. Treatment-emergent adverse events

CHARACTERISTIC	PLACEBO N=52		DFD-29 40MG N=53		DFD-29 20MG N=48		DOX 40MG N=48		OVERALL N=201	
Subject with any TEAE, n	35		39		40		37		151	
TEAEs, n	113		140		142		143		538	
Related TEAEs	24		44		33		32		113	
SAEs	0		1		2		2		5	
Related SAEs	0		0		1		0		1	
RELATED SAES	**E**	**n**	**E**	**n**	**E**	**n**	**E**	**n**	**E**	**n**
Atrial fibrillation					1	1			1	1
Vertigo			2	2			2	1	4	3
Eyelids pruritus							1	1	1	1
Blurred vision							1	1	1	1
Abdominal discomfort/distension[a]			1	1	1	1			2	2
Abdominal pain/upper[a]	5	3	7	5	2	2	2	1	16	11
Anal pruritus					1	1			1	1
Constipation			1	1	1	1			2	2
Diarrhea	3	2	4	3	1	1			8	6
Dry mouth/tongue coated[a]			2	1	2	1			4	2
Dyspepsia			2	2			1	1	3	3
Flatulence					3	3			3	3
Gastric ulcer					1	1			1	1
Gastritis	1	1				1			2	2
GERD			1	1	1	1			2	2
Nausea			5	4	1	1			6	5
Chills					1	1			1	1
Fatigue			2	2	1	1			3	3
Generalized edema			1	1					1	1
Infections[a]					2	2			2	2
Procedural nausea							2	1	1	1
Blood creatine increase			1	1					1	1
Arthralgia/back pain/myalgia[a]	2	2	2	2			2	1	6	5
Balance/dizziness[a]	1	1			2	2			3	3
Dysgeusia					2	2			2	2
Head discomfort					1	1			1	1
Headache	1	1	9	3	2	2	13	2	25	8
Migraine							1	1	3	2
Sleep disorder			1	1					1	1
Throat tightness					1	1			1	1
Acne/rosacea/rash[a]	3	3			2	2	3	3	8	8
Angioedema							2	1	2	1
Diffuse alopecia							1	1	1	1
Eczema	1	1			1	1			2	2
Hyperhidrosis			1	1	1	1			2	2
Pruritus	1	1					1	1	2	2
Hyperpigmentation			1						1	1

*Safety population, N=201; [a]Combined events; E: events; n: number of subjects; GERD: gastroesophageal reflux disease; SAE: serious adverse event; TEAE: treatment-emergent adverse event

($p<0.0001$).

Safety assessment. The safety analysis included 201 subjects, of which 151 (75.12%) reported a TEAE (Table 2). TEAEs were primarily of mild-to-moderate intensity, unrelated to study treatment, and resolved during the study. The most commonly reported related TEAE was headache (25 reports from eight subjects; 4%). The most common gastrointestinal TEAEs were abdominal pain (5.5%), diarrhea (3%), and nausea (2.5%). Skin-related disorders were low with no reported pain indicating stinging or burning of rosacea. One incident of vulvovaginal mycotic infection was reported with DFD-29 20mg, and one incident of mild hyperpigmentation with DFD-29 40mg; location and color of this event was not recorded. Three subjects reported vertigo: one receiving doxycycline 40mg experienced two vertiginous events (one mild, one moderate), while two in the DFD-29 40mg group experienced one vertiginous event each (both mild).

There were five SAEs: one with DFD-29 40mg, two with DFD-29 20mg, and two with doxycycline 40mg; only one with DFD-29 20mg (atrial fibrillation) was considered related to treatment. Overall, seven subjects were withdrawn from treatment due to TEAEs: five for skin-related TEAEs, one for headache, and one for balance/head discomfort. The overall incidence of TEAEs was similar between treatment groups, with no obvious safety signals.

DISCUSSION

Rosacea is one of the most prevalent dermatologic conditions, with multiple topical treatment options.[14,28] The only approved systemic treatment for rosacea is sub-antimicrobial doxycycline 40mg.[23] Clinical trials have shown this treatment reduces the signs of PPR.[23,29] We tested the efficacy of oral DFD-29, a minocycline formulation predicted to be at sub-antimicrobial doses, and compared this with doxycycline 40mg as an active comparator.

To determine the recommended Phase II dose (RP2D), it was critical to identify a dose that would maintain minocycline below the predicted MIC for most bacterial species to obviate the risk of causing resistance. The MIC for antibacterial doses of minocycline (100mg/day) is predicted to be the same as for tetracycline and doxycycline.[30,31] The MIC threshold for doxycycline has been

reported as 1000ng/mL for doxycycline-susceptible bacteria, 2000–8000 ng/mL for *Propionibacterium acnes*, and 4000 ng/mL by the Clinical and Laboratory Standards Institute.[12,32–34]

While DFD-29 40mg has not been confirmed as a sub-antimicrobial dose, we used the MIC threshold of 1000 ng/mL established for doxycycline as the limit for antimicrobial activity. The highest mean minocycline plasma levels achieved with DFD-29 40 mg were 382.8 (SD 188.7) ng/mL and 337.7 (SD 95.5) ng/mL on Days 1 and 21, respectively, both below the levels of the threshold and doxycycline 40mg. Doxycycline 40mg has been shown to not cause resistance after nine months of daily treatment.[35] Minocycline has been reported to result in less resistance than doxycycline when used as an antibiotic (eg, CA-MRSA).[34,36,37] Consequently, our results suggest that DFD-29 plasma levels do not exceed the predicted antimicrobial threshold, and, therefore, indicate a reduced possibility of causing resistance.

The Phase II study demonstrated that DFD-29 40mg met both its co-primary endpoints, indicating that it is an effective treatment for rosacea. DFD-29 40mg showed double the efficacy seen with doxycycline 40mg in the number of subjects achieving an IGA of "clear" or "almost clear" (66% vs. 33%). This superior efficacy was robustly evident in both primary analyses and sensitivity analyses. DFD-29 20mg showed significantly greater efficacy compared to placebo, while showing similar treatment effects to doxycycline 40mg.

The efficacy of doxycycline 40mg for both co-primaries were similar to those achieved in their two Phase III trials (IGA of 0/1 for 30.7 percent and 14.8 percent subjects, and reductions in mean lesion count of ~10).[23,29] Doxycycline 40mg has been tested in multiple clinical trials enrolling subjects with moderate PPR, and eight to 40 inflammatory lesions at baseline. Reductions in lesion counts consistently ranged from 10 to14 lesions after 16 weeks of treatment.[29,38,39] DFD-29 40mg treatment resulted in a mean reduction of 19 papules and pustules over 16 weeks, significantly more than the mean reduction of 10.5 lesions achieved with doxycycline.

The only previously reported head-to-head comparison of doxycycline 40mg with minocycline used a 100mg minocycline immediate-release formulation over 16 weeks; treatments were considered noninferior with similar mean reductions in lesion counts (13 vs. 14, respectively). Interestingly, IGA treatment success (a secondary endpoint) was significantly higher with minocycline 100mg (60% vs. 18%; $p<0.001$).[24] Our study indicates that DFD-29 40 mg ER produced superior outcomes to doxycycline 40mg on both IGA success and lesion count reductions.

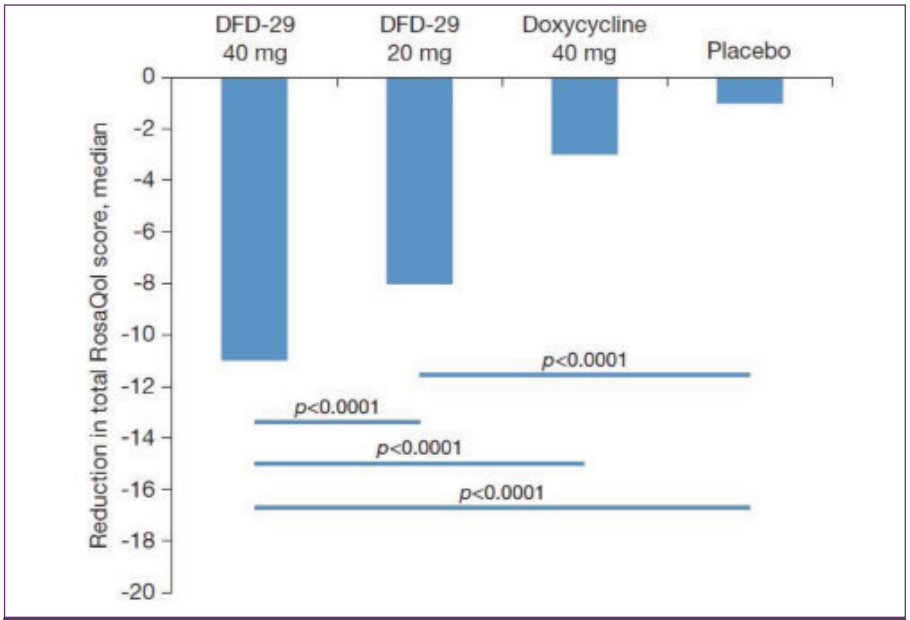

FIGURE 4. Median change in total RosaQoL score at Week 16. Mean score reduction from baseline shown. ITT population. Kruskal–Wallis test.

Studies of doxycycline 40mg compared with doxycycline 100mg have indicated similar clinical outcomes, maximum response being achieved with the doxycycline 40mg formulation.[39,40] Our results show that DFD-29 appears to have a dose effect, with the 40mg dose significantly improving outcomes over the 20mg dose. The outcomes demonstrated with DFD-29 40mg also appear to be the maximum reported for minocycline in well-controlled studies.

Any cutaneous condition affecting the face can have a negative impact on a patient's self-esteem and emotional state, often impacting social and work interactions. Therefore, it is important to assess the effect of any rosacea treatment on QoL. The RosaQoL is a validated questionnaire containing 21 rosacea-specific statements, encompassing emotion (11 statements), symptom (7 statements), and functioning (3 statements) to which subjects assign a value ranging from one (never) to five (all the time).[27] DFD-29 significantly lowered the total RosaQoL scores at 16 weeks. In addition, DFD-29 40mg reduced the score by significantly more than doxycycline 40mg.

Long-term use of antibiotics in rosacea is associated with yeast infections, gastrointestinal distress, photosensitivity, and vertigo.[32] Minocycline has been available since 1973 and has a long safety record. Early immediate-release formulations were associated with higher rates of vestibular AEs, thought to be due to greater passage across the blood–brain barrier, a consequence of superior lipophilicity.[41] The extended-release minocycline formulation approved for acne administered at 1mg/kg/day lists CNS AE rates of headache (23%), dizziness (9%), and vertigo (1%).[25] In this comparative study, rates of headache (4%) and vertigo (1.5%) were similar across treatment groups, with dizziness at just one percent. Other rare adverse events that have been associated with chronic, high-dose minocycline have been lupus-like erythematosus, hyperpigmentation, and hepatotoxicity.[42] Here, only one case of mild hyperpigmentation was reported with no autoimmune events.

Doxycycline has been associated with dose-related phototoxicity; however, these reports were associated with much higher doses of doxycycline (150mg/day) so were not expected in this study.[43] Here, only one case of mild

photosensitivity was reported with DFD-29 40mg.

A limitation in the understanding of the sub-antimicrobial levels is the lack of an established MIC for minocycline, as current product information for minocycline IR formulations utilizes tetracycline susceptibility data.[30] One criticism of antibacterial threshold data has been that MIC values and plasma concentration levels shown are mean values, while fast absorbers or slow metabolizers may exceed the threshold and cause resistance selection pressure. A long-term study of DFD-29 examining resistance levels would address these concerns.

CONCLUSION

Rosacea is a chronic inflammatory condition requiring long-term treatment. DFD-29 40mg provided superior efficacy to placebo and doxycycline 40mg in improving outcomes in papulopustular rosacea. PK assessment indicated that DFD-29 has a low risk of antimicrobial activity, maintaining levels below the predicted MIC threshold. DFD-29 was safe and well tolerated, with no evidence of the safety issues seen with high-dose minocycline. This is the first reported placebo and active comparator trial of a predicted subantimicrobial minocycline formulation. Further investigation of DFD-29 in Phase III trials is warranted.

ACKNOWLEDGMENTS

The authors thank the pharmacokinetics study investigator team of JOANNEUM RESEARCH, HEALTH – Institute for Biomedicine and Health Sciences, Graz, Austria: Reingard Raml, PhD (minocycline and doxycycline bioanalytical method validation, PK sample analysis); Bernd Tschapeller, MSc (data management); Thomas Augustin, PhD (statistics); and Karin Pickl, PhD (QA). Editorial assistance in the development of this manuscript was provided by Jodie Macoun, PhD, from CUBE Information.

REFERENCES

1. Gether L, Overgaard LK, Egeberg A, Thyssen JP. Incidence and prevalence of rosacea: a systematic review and meta-analysis. *Br J Dermatol*. 2018;179(2):282–289.
2. AAD. Skin conditions by the numbers. Rosacea. https://www.aad.org/media/stats-numbers. Accessed 16 Oct 2019.
3. Tan J, Schöfer H, Araviiskaia E, et al; RISE study group. Prevalence of rosacea in the general population of Germany and Russia – The RISE study. *J Eur Acad Dermatol Venereol*. 2016;30(3):428–434.
4. McAleer MA, Fitzpatrick P, Powell FC. Papulopustular rosacea: prevalence and relationship to photodamage. *J Am Acad Dermatol*. 2010;63(1):33–39.
5. Abram K, Silm H, Oona M. Prevalence of rosacea in an Estonian working population using a standard classification. *Acta Derm Venereol*. 2010;90(3):269–273.
6. Rueda LJ, Motta A, Pabón JG, et al. Epidemiology of rosacea in Colombia. *Int J Dermatol*. 2017;56(5):510–513.
7. Berg M, Lidén S. An epidemiological study of rosacea. *Acta Derm Venereol*. 1989;69(5): 419–423.
8. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol*. 2002;46(4):584–587.
9. Wilkin J, Dahl M, Detmar M, et al; National Rosacea Society Expert Committee. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2004;50:907–912.
10. Gallo RL, Granstein RD, Kang S, et al. Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2018;78:148–155.
11. Buddenkotte J, Steinhoff M. Recent advances in understanding and managing rosacea. *F1000Res*. 2018;3:7. pii: F1000 Faculty Rev-1885.
12. Fowler JF Jr. Anti-inflammatory dose doxycycline for the treatment of rosacea. *Expert Rev Dermatol*. 2007;2:523–531.
13. Rainer BM, Kang S, Chien AL. Rosacea: epidemiology, pathogenesis, and treatment. *Dermatoendocrinol*. 2017;9(1):e1361574.
14. Del Rosso JQ, Tanghetti E, Webster G, Stein Gold L, Thiboutot D, Gallo RL. Update on the management of rosacea from the American Acne & Rosacea Society (AARS). *J Clin Aesthet Dermatol*. 2019;12:17–24.
15. Cazalis J, Bodet C, Gagnon G, Grenier D. Doxycycline reduces lipopolysaccharide-induced inflammatory mediator secretion in macrophage and ex vivo human whole blood models. *J Periodontol*. 2008;79:1762–1768.
16. Ishikawa C, Tsuda T, Konishi H, et al. Tetracyclines modulate protease-activated receptor 2-mediated proinflammatory reactions in epidermal keratinocytes. *Antimicrob Agents Chemother*. 2009;53: 1760–1765.
17. Ueyama Y, Misaki M, Ishihara Y, Matsumura T. Effects of antibiotics on human polymorphonuclear leukocyte chemotaxis in vitro. *Br J Oral Maxillofac Surg*. 1994;32:96–99.
18. Hoyt JC, Ballering J, Numanami H, Hayden JM, Robbins RA. Doxycycline modulates nitric oxide production in murine lung epithelial cells. *J Immunol*. 2006;176:567–572.
19. Akamatsu H, Asada M, Komura J, et al. Effect of doxycycline on the generation of reactive oxygen species: a possible mechanism of action of acne therapy with doxycycline. *Acta Derm Venereol*. 1992;72:178–179.
20. Pruzanski W, Stefanski E, Vadas P, et al. Chemically modified non-antimicrobial tetracyclines inhibit activity of phospholipases A2. *J Rheumatol*. 1998;25:1807–1812.
21. Ryan ME, Usman A, Ramamurthy NS, et al. Excessive matrix metalloproteinase activity in diabetes: inhibition by tetracycline analogues with zinc reactivity. *Cur Med Chem*. 2001;8(3):305–316.
22. Griffin MO, Ceballos G, Villarreal FJ. Tetracycline compounds with non-antimicrobial organ protective properties: possible mechanisms of action. *Pharmacol Res*. 2011;63(2):102–107.
23. Oracea® (doxycycline USP) capsules 40 mg. [Prescribing information]. Fort Worth, TX: Galderma Laboratories; 2008.
24. van der Linden MMD, van Ratingen AR, van Rappard DC, et al. DOMINO, doxycycline 40 mg vs. minocycline 100 mg in the treatment of rosacea: a randomized, single-blinded, noninferiority trial, comparing efficacy and safety. *Br J Dermatol*. 2017;176(6):1465–1474.
25. Solodyn (minocycline hydrochloride) extended release tablets. [Prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals; 2017.
26. Jackson JM, Kircik LH, Lorenz DJ. Efficacy of extended-release 45 mg oral minocycline and extended-release 45 mg oral minocycline plus 15% azelaic acid in the treatment of acne rosacea. *J Drugs Dermatol*. 2013;12:292–298.
27. Nicholson K, Abramova L, Chren MM, et al. A pilot quality-of-life instrument for acne rosacea. *J Am Acad Dermatol*. 2007;57(2): 213–221.
28. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the

American Acne & Rosacea Society on the management of rosacea, part 2: a status report on topical agents. *Cutis*. 2013;92:277–284.
29. Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol*. 2007;56:791–802.
30. Minocin® (minocycline hydrochloride) 50 mg and 100 mg capsules. [Prescribing information]. Cranford, NJ: Triax Pharmaceuticals LLC; 2007.
31. Andrews JM. Determination of minimum inhibitory concentrations. *J Antimicrob Chemotherapy*. 2001;48(Suppl S1):5–16.
32. Steinhoff M, Vocanson M, Voegel JJ, et al. Topical ivermectin 10 mg/g and oral doxycycline 40 mg modified-release: current evidence on the complementary use of anti-inflammatory rosacea treatments. *Adv Ther*. 2016;33(9):1481–1501.
33. Ross JI, Snelling AM, Eady EA, et al. Phenotypic and genotypic characterization of antibiotic-resistant Propionibacterium acnes isolated from acne patients attending dermatology clinics in Europe, the U.S.A., Japan and Australia. *Br J Dermatol.* 2001;144:339–346.
34. Schwartz BS, Graber CJ, Diep BA, et al. Doxycycline, not minocycline, induces its own resistance in multidrug-resistant, community-associated methicillin-resistant Staphylococcus aureus clone USA300. *Clin Infect Dis*. 2009;48:1483–1484.
35. Preshaw PM, Novak MJ, Mellonig J, et al. Modified-release subantimicrobial dose doxycycline enhances scaling and root planing in subjects with periodontal disease. *J Periodontol*. 2008;79(3):440–452.
36. Carris NW, Pardo J, Montero J, Shaeer KM. Minocycline as a substitute for doxycycline in targeted scenarios: a systematic review. *Open Forum Infect Dis*. 2015;2(4):ofv178.
37. Lashinsky JN, Henig O, Pogue JM, Kaye KS. Minocycline for the treatment of multidrug and extensively drug-resistant A. baumannii: a review. *Infect Dis Ther*. 2017;6(2):199–211.
38. Fowler JF Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, usp monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. *J Drugs Dermatol*. 2007;6:641–645.
39. Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol*. 2008;7:573–576.
40. Theobald K, Bradshaw M, Leyden J. Anti-inflammatory dose doxycycline (40 mg controlled-release) confers maximum anti-inflammatory efficacy in rosacea. *Skinmed*. 2007;6:221–226.
41. Leyden JJ, Del Rosso JQ. Oral antibiotic therapy for acne vulgaris: pharmacokinetic and pharmacodynamic perspectives. *J Clin Aesthet Dermatol*. 2011;4:40–47.
42. Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic. *Br J Pharmacol*. 2013;169:337–352.
43. Del Rosso JQ. Oral doxycycline in the management of acne vulgaris: current perspectives on clinical use and recent findings with a new double-scored small tablet formulation. *J Clin Aesthet Dermatol*. 2015;8:19–26. JCAD